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10/647,449	08/25/2003	Manne Satyanarayana Reddy	BULK 3.0-026	1649
45776 7590 11/08/2007 DR. REDDY'S LABORATORIES, INC. 200 SOMERSET CORPORATE BLVD SEVENTH FLOOR, BRIDGEWATER, NJ 08807-2862			EXAMINER CHANG, CELIA C	
			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10/647,449	08/25/2003	REDDY ET AL.	BULK 3.0-026

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BRIDGEWATER, NJ 08807-2862

EXAMINER

Celia Chang

ART UNIT**PAPER**

1625

20071106

DATE MAILED:

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Commissioner for Patents

Attached, please find two corrected examiner's answer/supplemental examiner's answer.

Celia Chang
Primary Examiner
Art Unit 1625



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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/647,449
Filing Date: August 25, 2003
Appellant(s): REDDY ET AL.

Robert. A. Franks
For Appellant

(CORECTED)
EXAMINER'S ANSWER

This is in response to the appeal brief filed September 6, 2006 appealing from the Office action mailed March 6, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is mostly correct. However, the rejection of ground A. should include claim 39 as well, see inclusion in office action dated March. 6, 2006.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

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(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Evidence applied in rejection

5,132,924

Grell et al.

5-1995

*Grell et al. "Repaglinide and related hypoglycemic benzoic acid derivatives" J. Med. Chem. v.41, p.5219-5246 (1998)

*Brittain "Polymorphism in pharmaceutical solids" Marcel Dekker, p. 2, 178-179, 185, 219 (1999)

*Rouli "The right stuff" Chem. Eng. New. p.32-35 (2003)

*US Pharmacopia #23, national formulary #18 p.1843-1844 (1995)

State-of-the-art evidence rebutting appellants' argument

* EXHIBIT A comparison of IR

5,672,612

Ronsen et al.

9-1997

*Berstein "Polymorphism in molecular crystals" p., 253-254, 272-273 (2002)

*Davidovich et al. "Detection of polymorphism....." Am. Phar. Rev. v.7(1) pages 10, 12, 14, 16, 100 (2004)

*Polymorphism Wikipedia, encyclopedia on internet (2006)

*Baumann et al. "Reactions with microorganism....." Helvetica Chimica Acta 41, p.2362-79 (1958) with English abstract.

*Muzaffar et al. "Polymorphism and drug availability" J. Phar. 1(1) p.59-66 (1979)

*Jain et al. "Polymorphism in pharmacy" Indian Drugs 23(6) p. 315-329 (1986)

*Otsuka et al. "Effect of polymorphic forms....." Chem. Pharm. Bull. 47(6) p.852-856 (1999)

*Doelker "Thematic session. Crystalline modification....." Ann. Phar. Fr. 60:161-176 (2002) and English translation p.1-36.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims. The rejections are found in the office actions dated July 15, 2005 and Mar. 6, 2006 and hereby recited:

(A) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38 [*claim 39 has been canceled*], 40-48 [*claim 49 has been canceled*] are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,3,12,924 (recited on 1449).

See col. 89-90 the non-crystalline “residue” after vacuo of solvent ethanol. Noncrystalline solid is amorphous and the process is the same as the claimed (see col. 89-90, example 12) i.e. dissolving compound in ethanol, evaporating the solvent to separate the residue. (An inadvertent error was made in citing the location of the prior art and the error is hereby corrected. However, Appellants had no problem in locating the correct information as evidenced by the recitation in the brief on p.6).

Please note that it is well known in the art that there is only one amorphous product of a given material. (see Ulicky comprehensive dictionary of physical chemistry, p. 21, it was disclosed that solid can be subdivided into crystalline or amorphous. See concise encyclopedia chemistry, where it was defined that multiple crystalline forms are called polymorphs). Any x-ray diffraction of an amorphous material is only to show no diffraction or non-crystalline. Therefore, the incorporation of x-ray diffraction into the base claim does not change the product and anticipation is found.

(B) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 1, 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,132,924.

See col. 16, Figure 4 crystallized compound of the claims, form A, solid, and col. 33, form A is the low melting point form of the compound. Please note that one category of patentable invention is a "product". A novel or unobvious chemical product is identified first by its "chemical nature, i.e. elemental content and their ratios, i.e. the chemical identity. It was a well known "fact" that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Thus in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2). The term form III does not offer any demarcation of the product from the prior art crystalline product as represented by the compound name since form III or form A, B or C in the prior art are not notation known in the chemical art representing conventional characteristic in demarcating chemical products.

Please note that, the finding of anticipation is whether the claims and the prior art are "same identical" product not what physical parameters are used in claiming them. In so far as the instant claims are concern, to the extend the identifier being IR, the instant product and the prior art products are essentially the same i.e. compare figure 3 of the instant application and combined part I and II of figure 4 of US 5,132,924, thus, same product. Although 2 theta values and d-spacing are useful in identifying different crystalline forms, margin of error existed (see page 16, specification). Therefore, the single 2 theta pattern does not demarcate any product from another without multiple identifiers which when compared two forms clearly can demarcate each to be different products given margin in error.

(C) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 4-37, [*claim 39 has been canceled*], 50-51, 53-54, 56-57 [*claims 3, 52, 55 have been canceled*] are rejected under 35 U.S.C. 103(a) as being unpatentable over Grell et al. US 5,312,924 in view of Grell et al. J. Med. Chem (recited on 1449) and Brittain.

Determination of the scope and content of the prior art (MPEP §2141.01)

Grell et al. '942 disclosed compound that anticipated the base claims which was pointed out supra.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the Grell et al. disclosure and the instant dependent claims is that the physical property of the prior art product was not expressly included, or the process of making the products employed alternative solvents. Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules" (see Brittain p. 1-2).

Finding of prima facie obviousness—rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art would find the claims prima facie obvious because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existing different "morph" will display different physical properties such as X-ray diffraction pattern, melting point etc. (see Brittain p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court

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in *In re Cofer* 148 USPQ 268. *Ex parte Hartop* 139 USPQ 525, that products which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims disclosed known compound S-repaglinide form III, which is the same pure substance as the prior art, only has different arrangements and/or different conformations of the molecule. Mere difference in physical property is well known conventional variation for the same pure substance (see *Brittain* p.1-2), i.e. *prima facie* obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, easy of purification, preparation or synthesis, hygroscopicity, recovery or prevention of precipitation etc. (see p. 185).

The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see *Grell J. Med. Chem* p.5227). In absent of unexpected result it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product (please note that channel or associated solvates/hydrates are identical crystalline form with different physical properties because of the existence of solvents/water).

Even if the product of the instant application and the prior art differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property i.e. a mere variation in physical property which flows naturally with the changing form.

(D) Claims 8-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The analysis is applied to the instant case.

Nature of invention

Claims 8-18 are drawn to pharmaceutical composition comprising (S)-repaglinide as a solid wherein at least 80% by weight of said solid (S)-repaglinide is in crystalline form III.

The state of the art and predictability

The pharmaceutical formulation field is well aware that polymorphs when being formulated into compositions may undergo transformation thus, the particular form may not be the same form after processing, compressing etc. (see *Rouhi Chem. Eng. New*, see p. 34-35). Therefore, in absence of any description or factual evidence, how a crystalline form can be maintained in a composition to minimize transformation, no assumption can be made that the meta-stable polymorph will be maintained upon compression, tableting etc.

The amount of guidance and working examples

The specification lacks description and enablement that the pharmaceutical composition contains the claimed “form” without transformation. There is no factual basis provided in the specification as to support the transformation of less than 1-5% as found in claims 9-14. No description nor enabling support can be found as to how such limited transformation can be operable, i.e. temperature, pressure, carrier, etc.

In an article provided by applicants *tricky business*, it was evidenced that maintaining crystals in its desirable form is a tremendous effort. In the instant application, no example was found as to how a value of 80% form III was arrived in any solid composition; nor was any processing resulted in a composition comprising (S)-repaglinide as a solid wherein at least 80% by weight of said solid is in crystalline form III. Please note that, the transformation of any amount of the form III to other forms indicated the metastable nature of Form III. Therefore, absent of *any description or enablement* that the particular “form” or “X-ray” can be obtained/maintained in a “composition”, the deficiency of description and enablement as compared to the *art standard* described in applicants’ article *tricky business*, is self evident.

(10) Response to Argument

In response to **rejection (A)**, Appellants argued that:

it has long been the law that anticipation can properly be held only where a prior art document teaches each and every limitation of the rejected claim and inherency can not be established by probabilities or possibilities.

It is the Examiner’s position that:

A residue obtained, when (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-*n*-butyl}-aminocarbonylmethyl] benzoic acid in ethanol, was evaporated to remove solvent, is amorphous.

Two citations are hereby provided from the state of the art. The Berstein reference on p.254 clearly taught that “Amorphous pharmaceutical.....rapid solidification from the melt, lyophilization or spray drying, removal of solvents.....” The Ronsen ’612 reference taught that rotary evaporation as well as analogous spray drying will produce amorphous form which has essentially the same X-ray as the instant application figure 4 showing no peak in a powder X-ray diffraction.

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It has been clearly explained in the rejection that "Any x-ray diffraction of an amorphous material is only to show no diffraction or non-crystalline. Therefore, the incorporation of x-ray diffraction into the base claim does not change the product or process, and anticipation is found."

Besides, it has been clearly explained to appellants that all "amorphous" forms are not polymorphic, and *is not a polymorph* as explicitly recited in the Ulicky physical chemical dictionary.

In response to **rejection (B)**, Appellants argued that:

"...prior art IR was obtained on racemic repaglinide in methylene solution..."

"...in the form of X-ray diffraction patterns disclosed in the instant specification, clearly demonstrating that the instant and prior art products are different"

It is the Examiner's position that:

The IR are identical:

The side by side comparison of the IR for the instant product and the prior art product was provided as EXHIBIT A.

Please note that the IR of the prior art was obtained from form A solid not in solution.

There are two products having identical infrared data, one is called repaglinide form III, another is repaglinide form A solid; thus, the two products are identical.

The state of the art reference by Baumann et al. is provided to show that it is conventional skill well known in the chemical art that IR differentiates stereoisomers and racemates (see the difference in IR of S, R and meso/racemic compounds). Therefore, when two products are merely different by private naming but displayed identical IR, they are the same product, i.e. anticipated.

X-ray demonstrating different product:

X-ray diffraction pattern can provide information on the crystalline nature of a compound, X-ray diffraction pattern alone does not demarcate the identity of two products.

It is well recognized in the crystalline solid art that

Sometimes the difference in X-ray diffraction is very minor and must be carefully evaluated before a definitive conclusion is reach [on whether there is true polymorphs]
(US pharmacopia of record)

"...small changes in the powder X-ray patterns arise as artifacts rather than arising from polymorphism. We have found that many small changes in powder X-ray diffraction patterns are due to particle size/morphology or sample holder geometry"
(Davidovich)

In addition, it is hereby provided two visual comparison from the text book by Berstein, the figure on p.272 showed that two identical X-ray pattern, but one is the chemical compound

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pigment Yellow 14, wherein R is CH₃, while the other one is the pigment Yellow 63, R is Cl. Thus, identical X-ray displayed by different compounds. The figure on page 273 showed that two X-ray diffraction pattern collected on crystal and recrystal after melting. Although, there are new peaks, the authors concluded that "it may not be a pure modification" i.e. not a true polymorph.

X-ray diffraction, is a useful tool, but the results must be used with caution and it is not an absolute determination of true polymorphs especially, in the instant application, the diffraction patterns are obtained in a powdered X-ray which are known to have many artifacts which mislead the result absent other verification of the chemical identity and nature of the product. (see Davidovich)

Especially, in the instant case, the IR spectrum showed such close similarity, Appellants provided no factual evidence other than that Appellants named the product differently and there is Powder X-ray diffraction pattern. It is immaterial how other compounds and their polymorphs may be identifiable by their X-ray diffraction, each product is unique and empirical in its own way. In the instant case, Appellants provided no rebuttal to the fact that the two IR spectra are identical; but only argued that they have different name and they have other data. Such "other" information provided no evidence as to why the IR spectra are the same; nor how the products were different.

In response to **rejection (C)**, Appellants argued:

"...there is no teaching or suggestion in the cited references that (S)-repaglinide exists in other polymorphic forms.....Appellants alone, disclose that crystalline form II of (S)-repaglinide can be prepared from a solvent containing an aromatic hydrocarbon but does not include petroleum ether"

The Examiner's position is:

Appellants are unpersuasive as to the argument that the reference Grell et al. '924 did not suggest that repaglinide has polymorphic forms. Appellants' attention is drawn to col.32-33, example 11 wherein Form A, form B, Form C are made. Although the term "polymorph" was not used, one having ordinary skill in the art would have recognized that such transition of one form to another through melting and recrystallization; thus produced crystals which have lower and higher melting points are *polymorphic* crystals of the same compound.

Further, Appellants' attention is drawn to the fact that the claims are drawn to amorphous and polymorphic form III of repaglinide. Repaglinide form II was not under examination nor was the process of making form II in the claims. Please note that for the claimed invention, the amorphous form was made from alcoholic solvent systems (see claim 40); for form III, the solvent system is haloalkane (see claim 19). Nowhere in the claims is the issue of "aromatic hydrocarbon but not include petroleum ether" recited. Therefore, argument with respect to this limitation is unpersuasive.

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Contrary to Appellants' argument, the recited Grell et al. reference employed alcoholic solvents as well as haloalkanes in various process of making the product for example: in example 1, col. 16, line 49, tetrachloride was used; in example 2 col. 20, line 33, chloroform was used; in example 3, col. 21, line 40, dichlorobenzene was used; in example 11, col. 32, line 48, ethanol was used. Therefore, both polymorphic forms, how to prepare them, and the different solvent systems are found through out the reference. The species of specific solvents rendered the claims of using haloalkane and alcoholic system prima facie obvious. Especially, the prior art using the variation of *effect oriented elements* produced a product with identical IR, thus, further provided evidence that such modification is conventional routine technique to one having ordinary skill in the art and would be successful in obtaining the desirable products.

A state of the art reference from Wikipedia (encyclopedia over internet) further support the prima facie obvious nature of known pharmaceuticals having polymorphic forms because “...every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound”. In the instant case the very nature of repaglinide having polymorphic forms is disclosed in Grell '924, variations in process of making are disclosed in Grell '924, employing further variation flow naturally with the teaching of the prior art would proportionally increase the number of crystal forms, i.e. prima facie. In the instant case, the IR of form III is identical to the prior art form, in absence of careful comparative evaluation of single crystal X-ray, no clear factual evidence has been made of record that form III is not the same but only a variation of the prior art crystalline form A.

In response to **rejection (D)**, Appellants argued that:

“The subject matter of claims 8-18 is directed to a composition comprising crystalline form III.....that it is error to read such a limitation into the claims”

It is the Examiner's position that:

The argument by Appellants is very confusing. If the composition comprising repaglinide form III does not intend to mean “a composition that the form be maintained”, then what does it mean?

Preponderance of evidence in the state-of-the-art indicated that pharmaceutical compositions containing any particular crystalline form cannot be assumed but must be described and enabled with specificity and particularity. See for example:

Muzaffar et al. p.60 “At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form” And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. Translation page 3, "more than half of the pharmaceutical compounds exhibit polymorphism..... as such, they show at the solid state different physicalchemical properties which in turn may affect the technological and biopharmaceutical properties of active ingredients or excipients »

Translation page 34, "...crystalline state of the active principles, like that of the excipients, plays a *determining* role in the technological and biopharmaceutical characteristics of the solid or semi-solid pharmaceutical forms. The pharmaceutical scientist, like the chemist, therefore has the **requirement** to know as **completely** as possible the polymorphism.... »

Otsuke et al. p.852 « ...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process»

As observed in the enormous number of prior art that both the crystalline form of the active principle and what environment i.e. the process and excipients, it is in, must be completely known for one skilled in the art to practice such composition product.

Therefore, Appellants must first decide when the claims are drawn to "form III" does it mean it contains form III or not? A skilled person in the art would read the scope of claims 8-18 to must contain form III. This of course does not mean the active principle will exist indefinitely since all pharmaceutical products have a shelf life. On page 16 and 18 as recited by Appellants, the requirement of minimum amount of form III was described without any specific description of the environment i.e. excipients and processing parameters, that such form can be made into a composition. Such deficiency, as evidenced in the above state of the art teaching, provided insufficient description and enablement for the claims. Especially, there is no description as to under what circumstance the product will contain at least 80% i.e. a requirement to know as complete as possible.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons and factual evidence: The multiple state-of-the-art references submitted are well known facts but provided for Appellants' convenience that patentability of a "product" must be evaluated case by case based on the conventional knowledge known for that product. In the instant case:

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i) the claimed product does not have any difference in chemical identity i.e. compound vs hydrate of a compound, different in chemical identity;

ii) the claimed product has been known to have polymorphic forms and at least one physical characteristic, the IR, is identical;

iii) *powdered* X-ray alone does not decide on the novelty of a chemical product or novelty of a true morph;

iv) in absence of an operable composition with active principle, excipients and conditions of preparation clearly delineated, insufficient description was provided for the skilled artisan.

Therefore, the instant case is different from *Ex parte Havens*, *Ex parte Andrews* or *Ex parte Portmann*, because factual evidence indicated the natural flow of existence of new forms, obtaining new forms by spending time and money and new forms does not necessarily have any patentability advantage in either physical property (same IR) or formulation.

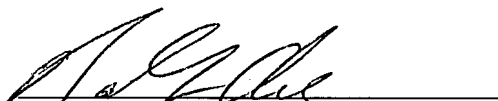
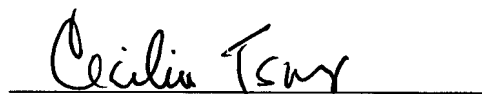
It is believed that the rejections should be sustained.

Respectfully submitted,



Celia Chang
Primary Examiner
Art Unit 1625

Conferees:


Janet Andres, SPE TC 1600
Cecilia Tsang, SPE, TC1600

Technology Center Director has approved of this corrected examiner's answer:


Christopher Low, Acting Director, Group 1600



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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/647,449
Filing Date: August 25, 2003
Appellant(s): REDDY ET AL.

R. A. FRANKS
For Appellant

(CORRECTED)
SUPPLEMENTAL EXAMINER'S ANSWER

This is in response to the REPLY appeal brief filed Jan. 27, 2007 responding to the Examiner's Answer mailed Nov. 30, 2006.

Some inadvertent error was noted in the examiner's answer which are hereby corrected:

--p.2, section(3) deletes the sentence "However, the rejection of ground A. should include claim 39 as well, see inclusion in office action dated March. 6, 2006.

--p.4, section (A) delete claim 39, delete claim 49,

--p. 6, section (C) delete claims 3, 39, 52, 55,

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The above correction is to correct the inadvertently included claim 3, 39, 49, 52, 55 in the examiner's amendment. Claim 39 was canceled by applicants in the Dec. 5, 2005 amendment. Claims 3, 49, 52, 55 were canceled by Mar. 6, 2006 amendment.

Please note the correction of claims in the "CORRECTED EXAMINER'S ANSWER".

All sections of the Examiner's Answer mailed together with this supplemental examiner's answer stayed the same with the supplemental to section (10) response to argument is hereby supplemented in response to the REPLY brief with further arguments.

(10) Response to Argument

(A) Appellants continuously discuss the issue of many compounds disclosed by Grell I are not the claimed compound. This is not relevant. The particular compounds of example 12 at col. 89-90 is (S)-(2-Ethoxy-4-[N-{ 1 -(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid). Therefore, the noncrystalline residue of col. 90, lines 5-6 is the exact "amorphous S-repaglinide" as claimed. A residue subject to "crystallization" is non-crystalline i.e. amorphous; this is a well-recognized fact. The objective factual evidence generally stated by Bernstein or Rosen only further evidenced that the same scientific phenomena is expected for the residue of col. 90, lines 5-6. The insistence by Appellants that Grell I is *silent* as to the form of (S)-repaglinide made by evaporation is erroneous. Because Grell I at col. 90, lines 5-6 implicitly disclosed that *"The organic extract is dried, filtered and evaporated down in vacuo. The evaporation residue is crystallized from ethanol/water"*. Were the "residue" is a crystal, it would have described as 'the crystal is recrystallised in ethanol water'. So implicitly, this statement clearly convey to one having ordinary skill in the art, the residue is "noncrystalline". All noncrystalline product is amorphous.

(B) Appellants continuously argued that the Grell I IR was taken in methylene chloride is irrelevant. It was clearly pointed out that Grell I, at col. 16, disclosed that figures 4-6 are taken from solid forms A-C.

Appellants newly presented argument that there seemed to have different lines between the prior art IR and the instant IR. As it has been clearly delineated all through prosecution that the Examiner has provided reasonable evidence that the "product" as claimed are essentially the

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same as the prior art. Grell I although did not identify whether the solid form is the (S) form, however, given the known merit of IR which can distinguish stereo isomers, were the Grell I form A not the (S) form, a different IR is expected. Appellants continuously argued with powder X-ray diffraction pattern for which as it was clearly evidenced in the art that such data without appropriate correction of artifacts and expert evaluation does not offer any rebuttal to the identity of two products being the same or not. Given the essentially same IR, Patent and Trademark Office bears lesser burden of proof, Appellants bears the burden of proof with reliable and reproducible factual evidence. Not mere arguments based on possession of additional physical data such as powdered X-ray without comparison.

(C) Appellants argued that the test of obviousness is *not whether the use of different solvents is expected to result in different forms, but, with claims 1, 2, 4-47, whether it would have been obvious to make a particular form.*

The standard of making a prima facie case of obviousness is whether one having ordinary skill in the art would be motivated by the prior art to modify the prior art and expects reasonable success that such modification would have the expected merits of the prior art (MPEP §2141-2143). It was clearly delineated in the rejection that the Grell et al. '924 disclosed polymorphic forms of the compounds, i.e. example 12, amorphous and recrystallization from ethanol/water. The Grell et al. '924 taught that the particular compound can have multiple forms (which have different physical properties) when crystallization conditions such as solvents, temperature etc. were affected (see example 3, col. 85-86, col. 16, forms A,B,C). The same Grell et al. also taught in the article J. Med. Chem. with analogous compounds that crystallization can be achieved with many common laboratory solvents (see pages 5226-5227 comments under the table). When one having ordinary skill in the art is asked, based on the recited reference, is one motivated to pick and choose some other solvent then petroleum ether of example 3, the answer is 'yes' because the same expert in the field said so (J. Med. Chem.). When one having ordinary skill in the art is asked that when choose a different solvent would one *reasonably expects a changed physical form*, the answer is 'yes' because factual nature of example 3 is that conversion of forms for this compound 'happens'.

The finding of prima facie obviousness is further evidenced by statements from the state-of-the-art references such as the Doelker reference that “*More than half of the pharmaceutical compounds exhibit polymorphism*”; or such as the Wikipedia encyclopedia that “*...every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound*”. Therefore, it is clear that, to one having ordinary skill in the pharmaceutical solid art, “a compound has polymorphic form” is an obvious variation of the crystalline compound. Just because no one has spend a lot of time and money in trying out every solvent to get every polymorphic forms does not offer any unexpectency of a polymorphic form. As it is evidenced by the state of the art textbook by Brittain, polymorphs strictly is the same pure substance. Such forms, upon spending more money and time will increase in number, i.e. is expected and obvious (see Whikipedia supra). Appellants offered no rebuttal that why by giving the variation form a name of “Form III” provided any reason to be unobvious.

(D) Appellants argued that “the Examiner believes that the instant specification lacks guidance....(p.13 reply brief) and it is an error “...to read such a limitation [that the claims requiring that the crystalline form III be maintained...] into the claims”.

Please note that all through prosecution, it was clearly delineated that the 112 issues were ***analyzed*** based on the preponderance of evidence from the state of the field, nowhere a personal believe was the standard for rejection.

It is very confusing as to what is the “claims” when the limitation “requiring that the crystalline form III be maintained” is not in the claim. What does claim 11 contain if the 99% Form III is not a requirement? Appellants further argued that the specification described that the composition should be monitored for form conversion and when the conversion to a point that no more form III, the composition is simply outside the scope of claims 8-18. This argument does not offer any factual support as to the instant “form III” would be *out of the ordinary and be spontaneously maintained* while others need invest tremendous effort, time and money for such endeavor (see Trick business of record).

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Responsive to THE REPLYBRIEF on Jan. 29, 2007, a supplemental Examiner's Answer is set forth above.

Appellant may file another reply brief in compliance with 37 CFR 41.41 within two months of the date of mailing of this supplemental examiner's answer. Extensions of time under 37 CFR 1.136(a) are not applicable to this two month time period. See 37 CFR 41.43(b)-(c)

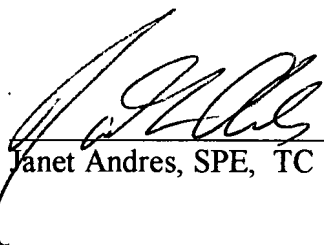
The application has been forwarded to the Board of Patent Appeals and Interferences for decision on the appeal.

Respectfully submitted,

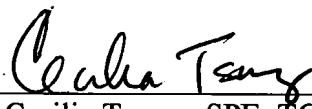


Celia Chang
Primary Examiner, AU 1625

Conferees:



Janet Andres, SPE, TC 1600



Cecilia Tsang, SPE, TC1600

Technology Center Director has approved this CORRECTED supplemental examiner's answer:



Christopher Low, Acting Director
Technology Center 1600